Application No. 10/506,748
Amendment Dated 03/14/2006
Reply to Office Action of 12/14/2005

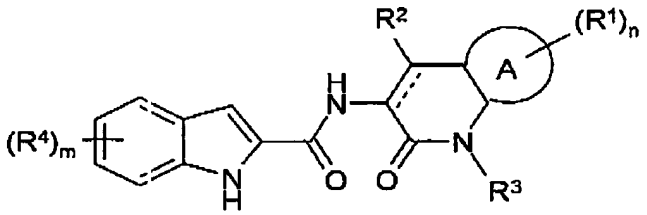
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-15. (Cancelled)

16. (New) A compound of formula (1):



(1)

wherein

---- is a single or double bond;

A is phenylene or heteroarylene;

m is 1;

n is 0, 1, or 2;

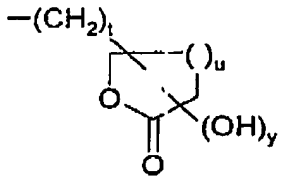
R^1 is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-C_{1-4}alkylcarbamoyl, *N*,*N*-$(C_{1-4}alkyl)_2$carbamoyl, sulphamoyl, *N*-C_{1-4}alkylsulphamoyl, *N*,*N*-$(C_{1-4}alkyl)_2$sulphamoyl, -$S(O)_b C_{1-4}$alkyl (wherein b is 0, 1, or 2), C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, hydroxyC_{1-4}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, and trifluoromethoxy; or

when n is 2, the two R^1 groups, together with the carbon atoms of A to which they are attached, may form a 4- to 7-membered ring, optionally containing 1 or 2 heteroatoms independently selected from O, S, and N, and optionally being substituted with one or two methyl groups;

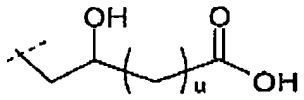
R^4 is chloro;

R^2 is hydrogen, hydroxy, or carboxy;

R^3 is selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, carbamoyl, C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, aryl, heterocyclyl, C_{1-4}alkyl (optionally substituted with 1 or 2 R^8 groups), and groups of the formulae B and B'



(B)



(B')

wherein y is 0 or 1, t is 0, 1, 2, or 3 and u is 1 or 2;

provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R^8 is independently selected from hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, C_{3-7}cycloalkyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1, or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1, or 2), aryl$S(O)_b$- (wherein b is 0, 1, or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1, or 2), benzyl$S(O)_b$- (wherein b is 0, 1, or 2), -N(OH)CHO, -C(=N-OH)NH_2, -C(=N-OH)NHC_{1-4}alkyl, -C(=N-OH)$N(C_{1-4}alkyl)_2$, -C(=N-OH)NHC_{3-6}cycloalkyl, -C(=N-OH)$N(C_{3-6}cycloalkyl)_2$, -COCOOR^9, -C(O)N$(R^9)(R^{10})$, -NHC(O)R^9, -C(O)N$HSO_2(C_{1-4}$alkyl), -NHSO_2R^9, $(R^9)(R^{10})NSO_2$-, -COCH_2OR^{11}, $(R^9)(R^{10})$N-, and -COOR^9;

R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted with 1 or 2 R^{13}), C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, trihalo(C_{1-4})alkyl, aryl, heterocyclyl, and heterocyclyl$(C_{1-4}$alkyl); or

R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring is optionally substituted on carbon with 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl, C_{1-4}alkoxy, and heterocyclyl, or the ring may be optionally substituted on two adjacent carbons with –O-CH_2-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH_2-O- group may be replaced by a methyl;

R^{13} is selected from hydroxy, halo, trihalomethyl, and C_{1-4}alkoxy; and

R^{11} is independently selected from hydrogen, C_{1-4}alkyl, and hydroxyC_{1-4}alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

17. (New) A compound of claim 16, wherein

R^3 is selected from hydrogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, carbamoyl, C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups, cyano(C_{1-4})alkyl, phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazoldinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino,

pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopydridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, and C_{1-4}alkyl (optionally substituted with 1 or 2 R^8 groups);
R^9 and R^{10} are independently selected from hydrogen, hydroxy, C_{1-4}alkyl (optionally substituted with 1 or 2 R^{13} groups), C_{3-7}cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C_{1-4})alkyl, trihalo C_{1-4}alkyl, aryl, heterocyclyl, and heterocyclyl(C_{1-4}alkyl); or
R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring is optionally substituted on carbon with 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl, and C_{1-4}alkoxy, or the ring may be optionally substituted on two adjacent carbons with $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;

R^8 is independently selected from hydroxy, C_{1-4}alkoxyC_{1-4}alkoxy, hydroxyC_{1-4}alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, C_{3-7}cycloalkyl, C_{1-4}alkanoyl, C_{1-4}alkoxy, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1, or 2), C_{3-6}cycloalkyl$S(O)_b$- (wherein b is 0, 1, or 2), aryl$S(O)_b$- (wherein b is 0, 1, or 2), heterocyclyl$S(O)_b$- (wherein b is 0, 1, or 2), benzyl$S(O)_b$- (wherein b is 0, 1, or 2), -N(OH)CHO, $-C(=N-OH)NH_2$, $-C(=N-OH)NHC_{1-4}$alkyl, $-C(=N-OH)N(C_{1-4}alkyl)_2$, $-C(=N-OH)NHC_{3-6}$cycloalkyl, $-C(=N-OH)N(C_{3-6}cycloalkyl)_2$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-C(O)NHSO_2(C_{1-4}alkyl)$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $(R^9)(R^{10})N-$, and $-COOR^9$;

R^{13} is selected from hydroxy, halo, trifluoromethyl, and C_{1-4}alkoxy; and

R^{11} is selected from hydrogen, C_{1-4}alkyl, and hydroxyC_{1-4}alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

18. (New) A compound of claim 16, wherein:

R^3 is selected from cyanoC_{1-4}alkyl and C_{1-4}alkyl (optionally substituted with1 or 2 R^8 groups);

R^8 is independently selected from hydroxy, phenyl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1, or 2), $-C(O)N(R^9)(R^{10})$, $-COOR^9$, $-C(O)NHSO_2Me$, $-C(=N-OH)NH_2$, $-C(=N-OH)NHC_{1-4}$alkyl, $-C(=N-OH)N(C_{1-4}alkyl)_2$, and $-NHSO_2R^9$; and

R^9 and R^{10} are independently selected from hydrogen, hydroxy, and C_{1-4}alkyl optionally substituted with R^{13} (wherein R^{13} is C_{1-4}alkoxy or hydroxy); or

R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring may be optionally substituted on carbon with 1 or 2 hydroxy groups or carboxy groups), or the ring may be optionally substituted on two adjacent carbons with $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

19. (New) A compound of claim 16, wherein:

R^3 is selected from cyano, C_{1-4}alkyl, and C_{1-4}alkyl (optionally substituted with 1 or 2 R^8 groups);

R^8 is independently selected from hydroxy, 2,2-dimethyl-1,3-dioxolan-4-yl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, tetrazolyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkyl$S(O)_b$- (wherein b is 0, 1, or 2), $-C(O)N(R^9)(R^{10})$, $-COOR^9$, $-C(O)NHSO_2Me$, and $-C(=N-OH)NH_2$; and

R^9 and R^{10} are independently selected from hydrogen, hydroxy, and C_{1-4}alkyl optionally substituted with R^{13} (wherein R^{13} is C_{1-4}alkoxy or hydroxy); or

R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring selected from piperidine, 4-hydroxypiperidine, pyrrolidine, 3,4-dihydroxypyrrolidine, and the dimethylacetal of 3,4-dihydroxypyrrolidine;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

20. (New) A compound of claim 16, wherein:
A is phenylene;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

21. (New) A compound of claim 16, wherein:
A is heteroarylene;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

22. (New) A compound of claim 16, wherein:
---- is a single bond;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

23. (New) A compound of claim 16 selected from:

5-chloro-*N*-[1-(methoxycarbonylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;

N-[1-(carboxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-5-chloroindole-2-carboxamide;

5-chloro-*N*-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-[{2-oxo-1-[2-oxo-2-(pyridin-2-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{1-[2-(methylthio)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{1-[2-(methylsulphinyl)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{1-[2-(methylsulphonyl)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-{2-oxo-1-[2-oxo-2-(1,3,4-thiadiazol-2-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(6-methylpyridin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-{2-oxo-1-[2-oxo-2-(pyridin-3-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(4-cyano-1*H*-pyrazol-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(4-methyl-1,3-thiazol-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(6-chloropyridin-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(3-hydroxypyridin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-(2-oxo-1-{2-oxo-2-[(pyridin-2-ylmethyl)amino]ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

5-chloro-*N*-{2-oxo-1-[2-oxo-2-(pyridin-4-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;

5-chloro-*N*-(1-{2-[(1-methyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-oxo-2-[(pyrazin-2-ylmethyl)amino]ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(6-fluoropyridin-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(2-hydroxypyrimidin-4-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-{2-oxo-1-[2-oxo-2-(pyrimidin-4-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1-ethyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-oxo-2-[(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)amino]ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(4-hydroxypyrimidin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(3-methylpyridin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(6-chloropyridazin-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1*H*-imidazol-2-ylmethyl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1-methyl-1*H*-pyrazol-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-{2-oxo-1-[2-oxo-2-(2*H*-tetrazol-5-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(3-ethyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(5-fluoropyridin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
N-(1-{2-[(6-bromopyridin-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-5-chloro-1*H*-indole-2-carboxamide;

5-chloro-*N*-[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-[(2,2-dimethyl-1,3-dioxan-5-yl)methyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-[3-hydroxy-2-(hydroxymethyl)propyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-[1-(2,3-dihydroxypropyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
5-chloro-*N*-[1-(3-hydroxy-2-oxopropyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(methylsulfonyl)amino]ethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
N-{1-[2-(acetylamino)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-5-chloro-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-[(trifluoroacetyl)amino]ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-[1-(3-hydroxypropyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
N-{1-[(2*Z*)-2-amino-2-(hydroxyimino)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-5-chloro-1*H*-indole-2-carboxamide;
5-chloro-*N*-(6-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*- indole-2-carboxamide; and
5-chloro-*N*-[6-(methyloxy)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

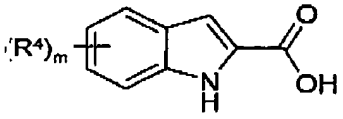
24. (New) A pharmaceutical composition which comprises a compound of claim 16, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, in association with a pharmaceutically acceptable diluent or carrier.

25. (New) A method for the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia, or obesity in a warm-blooded animal, comprising administering a compound of claim 16, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

26. (New) A method for the treatment of type 2 diabetes in a warm-blooded animal, comprising administering a compound of claim 16, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

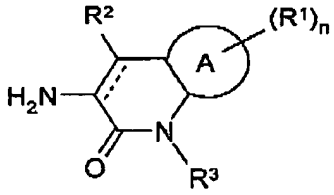
27. (New) A process for the preparation of a compound claim 16, which process comprises:

reacting an acid of the formula (2)



(2)

or an activated derivative thereof; with an amine of formula (3)



(3)

and thereafter if necessary

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups; or

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.